IN THE CLAIMS: See Listing of Claims. This listing will replace all prior versions of claims in the application.

REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action with appreciation. The previously issued Restriction Requirement has been withdrawn. Claims 12-23 remain pending in the application. The Office raises rejections under 35 USC § 112, first and second paragraphs, and under 35 USC § 102 and 35 USC § 103. The Office also raises obviousness-type double patenting rejections and a formalistic objection.

The Office acknowledges the priority claims to French Application FR 00.08791 and International Application PCT/FR01/02169 but states that certified copies of the priority documents have not been received by the Office. The Applicants respectfully submit that the instant application is a continuation application of US Serial No. 10/312,903. International Application PCT/FR01/02169 has been received by the Office and is available in the Image File Wrapper (IFW) system for US Serial No. 10/312,903 on the USTPO's website. Moreover, with the instant Response, the Applicants submit a certified copy of the French priority document (French Application FR 00.08791, filed July 6, 2000) and a certified translation thereof into English, thereby perfecting the claim to priority under 35 USC § 119, which claim was made upon filing.

Claims 15 and 17 are rejected for indefiniteness under 35 USC § 112, second paragraph, based on the limitation "in patent specification EP 0308341", which language is present in both claims. The Office notes that claims must stand alone to define an invention and that incorporation into the claims by express reference to anything other than another claim is not permitted. The Office also notes that incorporation of the specific process steps of EP 0308341 would overcome this rejection. With the instant Amendment, Claims 15 and 17 have been amended to incorporate the process steps disclosed in US Patent No. 4,914,214, an English language equivalent of EP 0308341, which is also cited (and incorporated by

reference) at page 2 of the instant specification. Reconsideration and withdrawal of the indefiniteness rejection is respectfully requested.

Claim 19 is rejected for lack of enablement under 35 USC § 112, first paragraph. It is the position of the Office that the specification, while being enabling for treating cardiovascular disease, does not reasonably provide enablement for all the conditions encompassed by Claim 19. With the instant Amendment, Claim 19 has been cancelled.

Claims 12-23 are rejected under 35 USC § 102(b) as being anticipated by Vincent, et al. (US Patent No. 4,914,214). It is the position of the Office that Vincent, et al. disclose (at Column 10) perindopril t-butylamine salt in crystalline form and that the disclosed compound anticipates the instant γ-crystalline form of perindopril t-butylamine salt.

Claims 20 and 22-23 are rejected under 35 USC § 102(e) as being anticipated by Guez, et al. (US Patent No. 6,653,336). It is the position of the Office that Guez, et al. disclose a pharmaceutical composition tablet comprising perindopril t-butylamine salt and a diuretic, such as indapamide, and that the disclosed pharmaceutical composition anticipates the instant pharmaceutical composition comprising the instant γ-crystalline form of perindopril t-butylamine salt and a diuretic, including indapamide.

The Office states that the only difference between the instant claims and the cited references is that Vincent, et al. and Guez, et al. are silent with respect to X-ray diffraction data, and it is the position of the Office that the claimed X-ray diffraction characteristics are inherent to the compounds disclosed in Vincent, et al. and Guez, et al.

The Office cites the Brittain reference (pages 348-361) to support its allegation that the instant γ-crystalline form is an inherent characteristic of the compound/composition disclosed in Vincent, et al. and Guez, et al. references. Based on the Brittain reference, the Office states that "[t]he process of preparing a

pharmaceutical composition will cause a specific crystalline form, if in the metastable state, to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure." See page 9 of the instant Office Action.

The Applicants respectfully submit that the Brittain reference also states (at page 348) that "[a]s tableting speeds increase towards commercial production, exposure times to stress decrease and one would anticipate even less chance for crystalline conversion. For the production of many substances, this situation is certainly true." The reference goes on to describe a study involving thirty-two (32) drugs known to exist in different polymorphic states. Of these thirty-two (32) drugs, eleven (11) appear to have been designated "transforming substances," and of these eleven (11) substances, detailed studies of tableting were conducted on only three (3) substances. The reference also discloses additional studies done on crystalline forms of other drugs as well as studies done on drugs containing amorphous material. The Office selective quotation of this comprehensive review of polymorphism is inappropriate and prejudicial to the applicant.

The Applicants respectfully submit that the data for specific compounds (which are structurally unrelated to the instantly claimed γ-crystalline form of perindopril t-butylamine salt) disclosed in the cited reference may not be extrapolated to the instant γ-crystalline form of perindopril t-butylamine salt, and that such data does not support the generalized conclusions of the Office with respect to polymorphs. The Applicants further submit that the Office argumentation directed to metastable conversion in formulating a pharmaceutical composition based on the Brittain reference is certainly not relevant to substance/compound and process Claims 12-19.

Moreover, in the preface, Brittain states that "[s]ince the middle of last century it has been noted that organic molecules can be obtained in more than one distinct crystal form..." and that "this book represents an attempt to summarize the major issues pertaining to the pharmaceutical aspects of polymorphism..." Thus, the Applicants respectfully submit that the Brittain reference, when taken as a whole, demonstrates that one skilled in the art would recognize that polymorphs are distinct substances

which possess distinct physical and structural properties. The very existence of the Brittain reference demonstrates that polymorphs are characterized as different substances.

The Applicants respectfully submit that perindopril t-butylamine salt disclosed in Vincent, et al. is crystallized directly from the reaction mixture, in contrast to the instant γ-crystalline form, which is produced by heating a solution of perindopril t-butylamine salt to reflux in ethyl acetate and then gradually cooling until crystallization is complete. Thus, although the Vincent, et al. reference discloses perindopril t-butylamine salt, it does not disclose or suggest the instant γ-crystalline form. See Vincent, et al. at column 9 (step 3D) wherein the isolation procedure is described as cooling the reaction mixture and then filtering off the product.

Moreover, the Applicants respectfully submit that, according to MPEP § 2112, in order to rely on a theory of inherency, the Office must provide "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112 also states that "the fact that a certain result or characteristic may occur or be present in the prior art is not enough to establish the inherency of that result or characteristic." As noted above, the Office has provided no support for the anticipation conclusion.

With this Response, the Applicants provide and make reference to International Published Application WO 2005/037788 (Singh, et al.) which discloses (at page 15, paragraph 2 and page 19, paragraph 4) that by reproducing the process for making perindopril t-butylamine salt disclosed in US Patent No. 4,914,214 (Vincent, et al.), in particular step 3D at column 9, a product other than the γ-crystalline form disclosed in International Published Application WO 01/87835 (an International equivalent of the instant application) is obtained. In other words, one skilled in the art has already published empirical data which rebuts the Office speculation.

Although Vincent, et al. disclose the preparation of a tert-butylamine salt of perindopril, the reference does not disclose the conditions which are required to

obtain the instant γ-crystalline form. In fact, step 3D of Vincent, et al. only discloses that tert-butylamine is added gradually, that refluxing is carried out until dissolution is complete, and that filtration, cooling, filtration and drying are carried out to produce perindopril t-butylamine salt. There is no disclosure with respect to the various possibilities for the cooling step, which could be, for example, rapid cooling or stepwise cooling.

The Applicants also provide a Declaration by Dr. Gérard COQUEREL, a scientist skilled in this particular art, which speaks to the 102/103 rejection. Specifically, the Declarant provides data which demonstrate and confirm that the instant γ-crystalline form is novel and non-obvious based on the cited references.

The Declarant has reproduced step 3D of Vincent, et al. (Experiment 1). The X-ray diffraction spectrum of the product obtained by the process disclosed in Vincent, et al. is different than the X-ray diffraction spectrum of the instant γ-crystalline form, demonstrating that the structure of the product of Vincent, et al. does not correspond to the instant γ-crystalline form. Moreover, the data provided also demonstrate that the cited references do not disclose the instantly claimed process nor a pharmaceutical composition comprising the instant γ-crystalline form of the tert-butylamine salt of perindopril.

Guez, et al. disclose pharmaceutical compositions comprised of perindopril and indapamide; however, Guez, et al. do not disclose that the perindopril t-butylamine salt used in the disclosed pharmaceutical compositions is in crystalline form, much less the instant γ-crystalline form. Thus, the Office has not demonstrated that the "allegedly inherent characteristic" necessarily flows from the teaching of the cited reference, and there is no disclosure in the Guez, et al. reference which suggests a pharmaceutical composition comprising the instant γ-crystalline form. The above-noted demonstrations establish that there is no prior disclosure of an γ-crystalline form of perindopril, and therefore, Guez, et al. could not possibly disclose or suggest the instant composition.

Therefore, the Applicants respectfully submit that the instant γ-crystalline form of perindopril t-butylamine salt and its pharmaceutical compositions are not anticipated by the respective disclosures of the Vincent, et al. and Guez, et al., references. Reconsideration and withdrawal of the anticipation rejections is respectfully requested.

Claims 12-23 are further rejected for obviousness under 35 USC § 103(a) based on Vincent, et al. in view of Guez, et al. or Brittain. It is the position of the Office that, since Vincent, et al. disclose a crystalline form of perindopril t-butylamine salt and Guez, et al. disclose a pharmaceutical composition comprising perindopril t-butylamine salt and a diuretic, such as indapamide, it would have been obvious to one skilled in the art to employ the compounds/compositions of Vincent, et al. and Guez, et al. to obtain the instant γ-crystalline form of perindopril t-butylamine salt and its pharmaceutical compositions.

The Office also states (at page 14 of the instant Office Action, citing In re Cofer, 148 USPQ 268 (CCPA)) that "...changing the form purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity, or characteristic was inherent in or rendered obvious by the prior art."

As noted above with respect to the anticipation rejection, the Applicants respectfully submit that MPEP § 2112 states that "the fact that a certain result or characteristic may occur or be present in the prior art is not enough to establish the inherency of that result or characteristic."

With respect to the Brittain reference, the Applicants respectfully reiterate that the data for specific compounds (which are structurally unrelated to the instantly claimed γ-crystalline form of perindopril t-butylamine salt) disclosed in the cited reference may not be extrapolated to the instant γ-crystalline form of perindopril t-butylamine salt, that such data does not support the generalized conclusions of the Office with respect to polymorphs, and that the Brittain reference when "taken as a whole" demonstrates that one skilled in the art would recognize that polymorphs are distinct substances which possess distinct physical and structural properties.

There is no disclosure in the cited references which would suggest to one skilled in the art that the conditions which are disclosed and claimed in the present application, rather than any other possible conditions, would produce the instant γ-crystalline form. As discussed above, Vincent, et al. do not disclose the instant γ-crystalline form of perindopril t-butylamine salt and the process disclosed in Vincent, et al. does not produce the instant γ-crystalline form.

Moreover, as disclosed in the instant specification at page 2, the instant γ-crystalline form provides the tert-butylamine salt of perindopril in a form that is sufficiently stable to allow it to be stored for a prolonged period.

The comparative stability study (Experiment 2) of the COQUEREL Declaration demonstrates that the instant γ-crystalline form of perindopril t-butylamine salt is stable after 37 days, under normal storage conditions, whereas the perindopril t-butylamine salt obtained by reproducing the process of the step 3D of Vincent, et al. is not stable after 1 month under the same conditions.

Moreover, the Applicants respectfully submit that, in the CCPA decision (In re Cofer) cited in the instant Office Action at pages 8 and 10, the CCPA held that

> [W]hether a given chemical compound or composition has the same usefulness as closely related materials may be an important consideration in determining obviousness under 35 USC 103. But it is only one consideration. We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the "subject matter as a whole" to be compared with prior art as are other properties of the material which make it useful.

Therefore, notwithstanding the instant demonstration of the superior and unexpected properties associated with the instant γ-crystalline form provided in the COQUEREL Declaration, the Applicants further submit that the Office has not made the required demonstration, i.e., that the cited references teach or suggest "the particular structure or form" of the instant γ-crystalline form as well as "suitable methods of obtaining that structure or form" to establish a case of *prima facie* obviousness.

The Applicants also respectfully submit that in two non-precedential decisions by the BPAI (Ex Parte Gala and Dibenedetto – Appeal No. 2001-0987; Application 09/169,109 and Ex Parte Havens – Appeal No. 2001-0091; Application No. 08/732,254), the Board found that a new crystalline form was not anticipated nor rendered obvious by either the earlier disclosure of another distinct polymorph (Ex Parte Gala and Dibenedetto) or the compound *per se* (Ex Parte Havens). These recent decisions, although non-precedential, are consistent with the holding in Cofer.

Thus, the Applicants respectfully submit that the instant γ-crystalline form as well as the instant pharmaceutical compositions comprising the γ-crystalline form are not rendered obvious by the disclosure of the Vincent, et al., Guez, et al., and Brittain references. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

Claims 12-23 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1,8-9, and 11-12 of co-pending application US Serial No. 11/052,489 or over Claims 22-23 and 25-26 of co-pending application US Serial No. 10/792,355. It is the position of the Office that, although the conflicting claims are not identical, they are not patentably distinct since the instant claims as well as the claims in the co-pending applications are directed to crystalline forms of perindopril t-butylamine salt.

The Applicants respectfully submit that one skilled in the chemical arts would recognize that compound such as perindopril may exist in distinct crystalline forms (i.e., polymorphs). As discussed above, the Brittain reference demonstrates that one skilled in the art would also recognize that different, crystalline forms of the

compound would possess distinct physical properties, and it has also been established by the discussion above that the Office and the courts recognize that distinct crystalline forms may represent patentably distinct subject matter.

Moreover, there is nothing in co-pending application US Serial No. 11/052,489 or in co-pending application US Serial No. 10/792,355 to suggest the particular γ-crystalline form nor a suitable method for obtaining the instant γ-crystalline form. Thus, the instant γ-crystalline form of perindopril t-butylamine salt is patentably distinct from the limited disclosures of the α-crystalline and β-crystalline forms of perindopril t-butylamine salt. Reconsideration and withdrawal of the obviousness-type double-patenting rejection is respectfully requested.

* * * * *

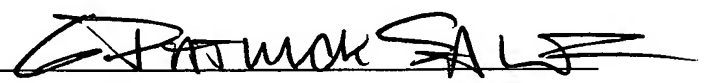
Accordingly, entry of the COQUEREL Declaration and the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: 

G. PATRICK SAGE

Dated: December 7, 2006
Customer No.: 25,666
Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030

Enclosure: COQUEREL Declaration; Form PTO-1449 and Accompanying Reference; Fee for Three (3) Month Extension; Certified Copy of French Priority Application FR 00.08791and Certified Translation thereof into English; Listing of Claims; and Postal Card Receipt

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THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.